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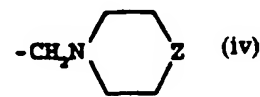
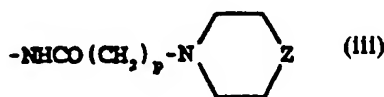
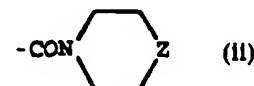
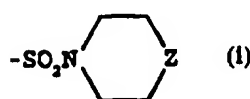
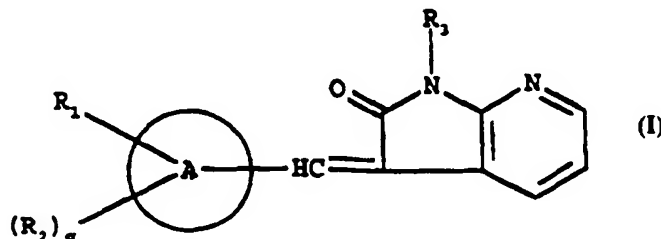
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(71) Applicant (for all designated States except US): PHARMACIA S.P.A. [IT/IT]; Via Robert Koch, 1.2, I-20152 Milan (IT).			
(72) Inventors; and (75) Inventors/Applicants (for US only): BUZZETTI, Franco [IT/IT]; Via della Gallarana, 4, I-20052 Monza (IT). BRASCA, Gabriella, Maria [IT/IT]; Via Dante Alighieri, 15, I-20090 Cusago (IT). LONGO, Antonio [IT/IT]; Via N.A. Porpora, 160, I-20131 Milan (IT). BALLINARI, Dario [IT/IT]; Via C. Jannozzi, 8, I-20097 San Donato Milanese (IT).			

(54) Title: SUBSTITUTED 3-ARYLIDENE-7-AZAOXINDOLE COMPOUNDS AND PROCESS FOR THEIR PREPARATION

(57) Abstract

The present invention relates to compound of formula (I) wherein A is benzene, naphthalene, 5,6,7,8-tetrahydronaphthalene, quinoline, isoquinoline, indole or 7-azaindole; R<sub>1</sub> is -H, -CN, -SO<sub>2</sub>R<sub>4</sub>, -SO<sub>2</sub>NHR<sub>5</sub>, (i), -COOR<sub>6</sub>, -CONHCH<sub>2</sub>(CHOH)<sub>n</sub>CH<sub>2</sub>OH, (ii), -NR<sub>7</sub>R<sub>8</sub>, -N(CH<sub>2</sub>CH<sub>2</sub>OH)<sub>2</sub>, -NHCH<sub>2</sub>(CHOH)<sub>n</sub>CH<sub>2</sub>OH, -NHCONH<sub>2</sub>, -NH-C(NH<sub>2</sub>)-NH<sub>2</sub>, -NHCO(CH<sub>2</sub>OH)<sub>n</sub>CH<sub>2</sub>OH, (iii), -NHSO<sub>2</sub>R<sub>9</sub>, -OR<sub>10</sub>, -OCH<sub>2</sub>(CHOH)<sub>n</sub>CH<sub>2</sub>OH, -OOC(CH<sub>2</sub>OH)<sub>n</sub>CH<sub>2</sub>OH, -OPO(OH)<sub>2</sub>, -CH<sub>2</sub>NH<sub>2</sub>, -C(NH<sub>2</sub>)-NH<sub>2</sub>, -CH<sub>2</sub>NHC(NH<sub>2</sub>)-NH<sub>2</sub>, (iv), -CH<sub>2</sub>OH, -CH<sub>2</sub>OOC(CH<sub>2</sub>OH)<sub>n</sub>CH<sub>2</sub>OH, -CH<sub>2</sub>OPO(OH)<sub>2</sub> or -PO(OH)<sub>2</sub>; R<sub>2</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, or hydroxy; R<sub>3</sub> is -H or C<sub>1</sub>-C<sub>6</sub> alkyl; R<sub>4</sub> is -H, C<sub>1</sub>-C<sub>6</sub> alkyl or -CH<sub>2</sub>(CHOH)<sub>n</sub>CH<sub>2</sub>OH; R<sub>5</sub> is -H, C<sub>1</sub>-C<sub>6</sub> alkyl, -CH<sub>2</sub>(CHOH)<sub>n</sub>CH<sub>2</sub>OH or -(CH<sub>2</sub>)<sub>m</sub>NMe<sub>2</sub>; R<sub>6</sub> is -H, C<sub>1</sub>-C<sub>6</sub> alkyl or -CH<sub>2</sub>(CHOH)<sub>n</sub>CH<sub>2</sub>OH; each of R<sub>7</sub> and R<sub>8</sub> independently is -H or C<sub>1</sub>-C<sub>6</sub> alkyl; R<sub>9</sub> is methyl or tolyl; R<sub>10</sub> is -H, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>2</sub>-C<sub>6</sub> alkanoyl; Z is >CH<sub>2</sub>, >O, >NH or >NCH<sub>2</sub>CH<sub>2</sub>OH; n is zero or 1; m is 2 or 3; p is 1, 2 or 3; q is zero, 1 or 2; and the pharmaceutically acceptable salt thereof, for use as tyrosine kinase inhibitors.



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WO 96/16964

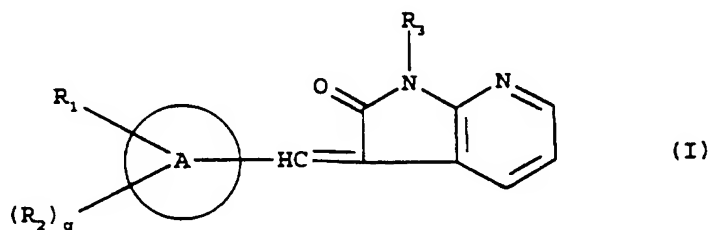
PCT/EP95/04247

-1-

# SUBSTITUTED 3-ARYLIDENE-7-AZAOXINDOLE COMPOUNDS AND PROCESS FOR THEIR PREPARATION

5 The present invention relates to 3-arylidene-7-azaoxindole compounds, to a process for their preparation, to pharmaceutical compositions containing them and to their use as therapeutic agents.

10 The present invention provides compounds having the following general formula (I)



wherein

A is benzene, naphthalene, 5,6,7,8,-tetrahydronaphthalene, quinoline, isoquinoline, indole or 7-azaindole;

15  $R_1$  is -H, -CN,  $-SO_3R_4$ ,  $-SO_2NHR_5$ ,  $-SO_2N$  (cyclohexyl) Z,  $-COOR_6$ ,  
 $-CONHCH_2(CHOH)_nCH_2OH$ ,  $-CON$  (cyclohexyl) Z,  $-NR_7R_8$ ,  $-N(CH_2CH_2OH)_2$ ,  
 $-NHCH_2(CHOH)_nCH_2OH$ ,  $-NHCONH_2$ ,  $-NH-C(NH_2)=NH$ ,  
 $-NHCO(CH_2)_p-N$  (cyclohexyl) Z,  $-NHCO(CHOH)_nCH_2OH$ ,  $-NHCO_2R_9$ ,  $-OR_{10}$ ,  
20  $-OCH_2(CHOH)_nCH_2OH$ ,  $-OOC(CHOH)_nCH_2OH$ ,  $-OPO(OH)_2$ ,  $-CH_2NH_2$ ,  
 $-C(NH_2)=NH$ ,  $-CH_2NHC(NH_2)=NH$ ,  $-CH_2N$  (cyclohexyl) Z,  $-CH_2OH$ ,

WO 96/16964

PCT/EP95/04247

-2-

$-\text{CH}_2\text{OOC}(\text{CHOH})_n\text{CH}_2\text{OH}$ ,  $-\text{CH}_2\text{OPO}(\text{OH})_2$  or  $-\text{PO}(\text{OH})_2$ ;

$\text{R}_2$  is  $\text{C}_1\text{-C}_6$  alkyl, halogen, or hydroxy;

$\text{R}_3$  is  $-\text{H}$  or  $\text{C}_1\text{-C}_6$  alkyl;

$\text{R}_4$  is  $-\text{H}$ ,  $\text{C}_1\text{-C}_6$  alkyl or  $-\text{CH}_2(\text{CHOH})_n\text{CH}_2\text{OH}$ ;

5  $\text{R}_5$  is  $-\text{H}$ ,  $\text{C}_1\text{-C}_6$  alkyl,  $-\text{CH}_2(\text{CHOH})_n\text{CH}_2\text{OH}$  or  $-(\text{CH}_2)_m\text{NMe}_2$ ;

$\text{R}_6$  is  $-\text{H}$ ,  $\text{C}_1\text{-C}_6$  alkyl or  $-\text{CH}_2(\text{CHOH})_n\text{CH}_2\text{OH}$ ;

each of  $\text{R}_7$  and  $\text{R}_8$  independently is  $-\text{H}$  or  $\text{C}_1\text{-C}_6$  alkyl;

$\text{R}_9$  is methyl or tolyl;

$\text{R}_{10}$  is  $-\text{H}$ ,  $\text{C}_1\text{-C}_6$  alkyl or  $\text{C}_2\text{-C}_6$  alkanoyl;

10  $\text{Z}$  is  $>\text{CH}_2$ ,  $>\text{O}$ ,  $>\text{NH}$  or  $>\text{NCH}_2\text{CH}_2\text{OH}$ ;

$n$  is zero or 1;

$m$  is 2 or 3;

$p$  is 1, 2 or 3;

$q$  is zero, 1 or 2;

15 and the pharmaceutically acceptable salt thereof.

The invention includes within its scope all the possible isomers, stereoisomers, in particular *Z*- and *E*-isomers, as well as the metabolites and the metabolic precursors or  
20 bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I).

The substituents  $\text{R}_1$  and  $\text{R}_2$  may be independently on either of the ring moieties when A is bicyclic.

The azaoxindolylidene substituent is preferably linked to  
25 position 1 or 2 when A is naphthalene or 5,6,7,8-tetrahydronaphthalene, to position 4 or 5 when A is quinoline, to position 1 or 3 when A is isoquinoline, to position 3 when A is indole, or 7-azaindole.

The  $\text{R}_1$  substituent with reference to the azaoxindolylidene  
30 substituent is preferably linked to the other ring moiety

WO 96/16964

PCT/EP95/04247

-3-

when A is naphthalene, 5,6,7,8-tetrahydronaphthalene, quinoline, isoquinoline, indole or azaindole.

The alkyl group and the alkyl moiety in the alkanoyl group may be branched or straight alkyl chains.

- 5 A C<sub>1</sub>-C<sub>6</sub> alkyl group is preferably a C<sub>1</sub>-C<sub>4</sub> alkyl group, e.g. methyl, ethyl, propyl, isopropyl, butyl, sec-butyl or t-butyl, in particular methyl or ethyl.

A C<sub>2</sub>-C<sub>6</sub> alkanoyl group is preferably a C<sub>2</sub>-C<sub>3</sub> alkanoyl group, in particular acetyl or propionyl.

- 10 A halogen is preferably fluorine, chlorine or bromine, in particular fluorine.

Pharmaceutically acceptable salts of the compounds of the invention include acid addition salts with inorganic, e.g. nitric, hydrochloric, hydrobromic, sulfuric, perchloric and

- 15 phosphoric acids or organic, e.g. acetic, trifluoroacetic, propionic, glycolic, lactic, oxalic, malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic and salicylic acids, and salts with inorganic, e.g. alkali metal, especially sodium or potassium, bases or alkaline-  
20 earth metal, especially calcium or magnesium, bases or with organic bases, e.g. acyclic or cyclic amines, preferably triethylamine or piperidine.

As stated above, the present invention also includes within its scope pharmaceutically acceptable bio-precursors

- 25 (otherwise known as pro-drugs) of the compounds of formula (I), i.e. compounds which have a different formula to formula (I) above but which, nevertheless, upon administration to a human being are converted directly or indirectly in vivo into a compound of formula (I).

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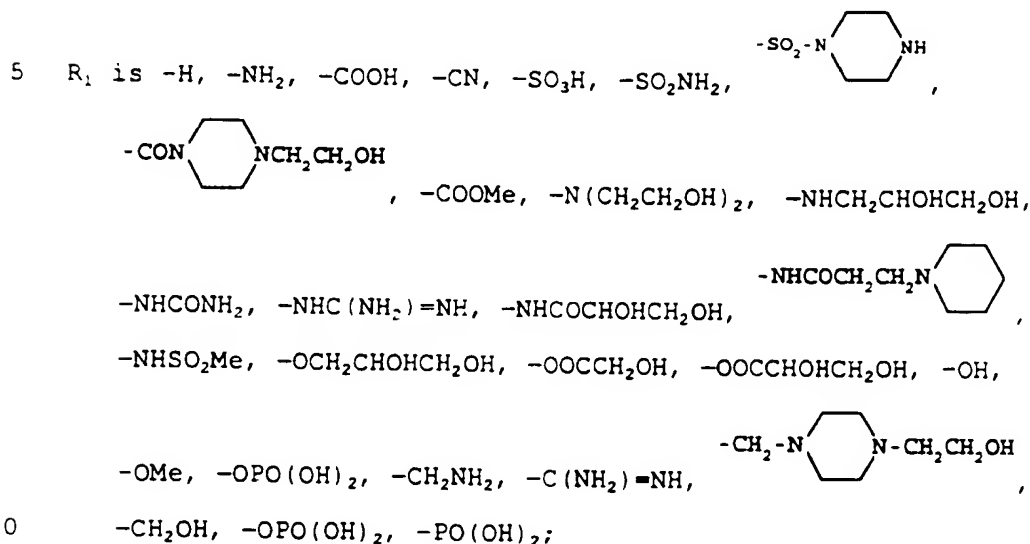
WO 96/16964

PCT/EP95/04247

-4-

Preferred compounds of the invention are the compounds of formula (I), wherein

A is benzene, 5,6,7,8-tetrahydronaphthalene, quinoline, indole or 7-azaindole;



$R_2$  is C<sub>1</sub>-C<sub>6</sub> alkyl or hydroxy;

$R_3$  is -H;

q is zero, 1 or 2;

and the azaoxindolylidene substituent is preferably linked

15 to position 1 or 2 when A is naphthalene or 5,6,7,8-tetrahydronaphthalene, to position 4 or 5 when A is quinoline, to position 3 when A is indole or 7-azaindole, whereas the  $R_1$  substituent is preferably linked to the other ring moiety when A is bicyclic, and the

20 pharmaceutically acceptable salts thereof.

Examples of specific compounds of the invention are the following compounds, which, when appropriate may be either Z- or E-diastereomers or 2,E-mixtures of said

25 diastereomers:

WO 96/16964

PCT/EP95/04247

-5-

- 1) 3-[(3,5-di-tert-butyl-4-hydroxyphenyl)methylene]-7-  
azaaxindole;
- 2) 3-[(4-hydroxyphenyl)methylene]-7-azaaxindole;
- 3) 3-[4-(2,3-dihydroxypropoxy)phenylmethylene]-7-  
5 azaaxindole;
- 4) 3-[(4-methoxyphenyl)methylene]-7-azaaxindole;
- 5) 3-[(4-aminophenyl)methylene]-7-azaaxindole;
- 6) 3-[(4-diethanolaminophenyl)methylene]-7-azaaxindole;
- 7) 3-[(4-glyceroylamidophenyl)methylene]-7-azaaxindole;
- 10 8) 3-[4-(3-piperidinopropionylamino)phenyl)methylene]-7-  
azaaxindole;
- 9) 3-[(4-ureidophenyl)methylene]-7-azaaxindole;
- 10) 3-[(4-mesylaminophenyl)methylene]-7-azaaxindole;
- 11) 3-[(4-guanidinophenyl)methylene]-7-azaaxindole;
- 15 12) 3-[(4-sulfophenyl)methylene]-7-azaaxindole;
- 13) 3-[(4-N,N-piperazinylsulfamoylphenyl)methylene]-7-  
azaaxindole;
- 14) 3-[(4-sulfamoylphenyl)methylene]-7-azaaxindole;
- 15) 3-[(4-aminomethylphenyl)methylene]-7-azaaxindole;
- 20 16) 3-[(4-amidinophenyl)methylene]-7-azaaxindole;
- 17) 3-[(4-phosphonooxyphenyl)methylene]-7-azaaxindole;
- 18) 3-[(4-carboxyphenyl)methylene]-7-azaaxindole;
- 19) 3-[(4-carbomethoxyphenyl)methylene]-7-azaaxindole;
- 20) 3-[(4-hydroxymethylphenyl)methylene]-7-azaaxindole;
- 25 21) 3-[4-(2,3-dihydroxypropylamino)phenylmethylene]-7-  
azaaxindole;
- 22) 3-[(4-glycoloyloxyphenyl)methylene]-7-azaaxindole;
- 23) 3-[(4-phosphonophenyl)methylene]-7-azaaxindole;
- 24) 3-[(4-hydroxyethylpiperazin-1-ylmethyl)phenyl  
30 methylene]-7-azaaxindole;

WO 96/16964

PCT/EP95/04247

-6-

- 25) 3-[4-(N,N-(4'-hydroxyethyl)piperazinylcarbamoyl)phenyl  
methylene]-7-azaoxindole;
- 26) 3-[4-sulfophenylmethylene]-7-azaoxindole sodium salt;
- 27) 3-[4-aminophenylmethylene]-7-azaoxindole hydrochloride;
- 5 28) 3-[4-aminophenylmethylene]-7-azaoxindole trifluoro-  
acetate;
- 29) 3-[(3-hydroxy-5,6,7,8-tetrahydronaphth-2-yl)methylene]-  
7-azaoxindole;
- 30) 3-[(1,4-dihydroxy-5,6,7,8-tetrahydronaphth-2-yl)  
10 methylene]-7-azaoxindole;
- 31) 3-[3-(2,3-dihydroxypropoxy)-5,6,7,8-tetrahydronaphth-2-  
yl)methylene]-7-azaoxindole;
- 32) 3-[(3-methoxy-5,6,7,8-tetrahydronaphth-2-yl)methylene]-  
7-azaoxindole;
- 15 33) 3-[(4-amino-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-  
azaoxindole;
- 34) 3-[(4-diethanolamino-5,6,7,8-tetrahydronaphth-1-yl)  
methylene]-7-azaoxindole;
- 35) 3-[(4-glyceroylamido-5,6,7,8-tetrahydronaphth-1-yl)  
20 methylene]-7-azaoxindole;
- 36) 3-[4-(3-piperidinopropionylamino)-5,6,7,8-tetrahydro  
naphth-1-yl)methylene]-7-azaoxindole;
- 37) 3-[(4-ureido-5,6,7,8-tetrahydronaphth-1-yl)methylene]-  
7-azaoxindole;
- 25 38) 3-[(4-mesylamino-5,6,7,8-tetrahydronaphth-1-yl)  
methylene]-7-azaoxindole;
- 39) 3-[(4-guanidino-5,6,7,8-tetrahydronaphth-1-yl)  
methylene]-7-azaoxindole;
- 40) 3-[(4-sulfo-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-  
30 azaoxindole;



WO 96/16964

PCT/EP95/04247

-7-

- 41) 3-[(4-N,N-piperazinylsulfamoyl-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-azaoxindole;
- 42) 3-[(4-sulfamoyl-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-azaoxindole;
- 5 43) 3-[(4-aminomethyl-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-azaoxindole;
- 44) 3-[(4-amidino-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-azaoxindole;
- 45) 3-[(4-phosphono-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-azaoxindole;
- 10 46) 3-[(4-carboxy-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-azaoxindole;
- 47) 3-[(4-carbomethoxy-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-azaoxindole;
- 15 48) 3-[(4-quinolyl)methylene]-7-azaoxindole;
- 49) 3-[(8-hydroxy-5-quinolyl)methylene]-7-azaoxindole;
- 50) 3-[(8-sulfo-5-quinolyl)methylene]-7-azaoxindole;
- 51) 3-[(8-sulfamoyl-5-quinolyl)methylene]-7-azaoxindole;
- 52) 3-[(8-aminomethyl-5-quinolyl)methylene]-7-azaoxindole;
- 20 53) 3-[(2-methyl-3-indolyl)methylene]-7-azaoxindole;
- 54) 3-[(3-indolyl)methylene]-7-azaoxindole;
- 55) 3-[(5-hydroxy-3-indolyl)methylene]-7-azaoxindole;
- 56) 3-[(5-methoxy-3-indolyl)methylene]-7-azaoxindole;
- 57) 3-[(5-amino-3-indolyl)methylene]-7-azaoxindole;
- 25 58) 3-[(5-diethanolamino-3-indolyl)methylene]-7-azaoxindole;
- 59) 3-[(5-glyceroylamido-3-indolyl)methylene]-7-azaoxindole;
- 60) 3-[(5-(3-piperidinopropionylamino)-3-indolyl)methylene]-7-azaoxindole;
- 30 61) 3-[(5-ureido-3-indolyl)methylene]-7-azaoxindole;

WO 96/16964

PCT/EP95/04247

-8-

- 62) 3-[(5-mesylamino-3-indolyl)methylene]-7-azaoxindole;
  - 63) 3-[(5-guanidino-3-indolyl)methylene]-7-azaoxindole;
  - 64) 3-[(5-sulfo-3-indolyl)methylene]-7-azaoxindole;
  - 65) 3-[(5-N,N-piperazinylsulfamoyl-3-indolyl)methylene]-7-  
5 azaoxindole;
  - 66) 3-[(5-sulfamoyl-3-indolyl)methylene]-7-azaoxindole;
  - 67) 3-[(5-aminomethyl-3-indolyl)methylene]-7-azaoxindole;
  - 68) 3-[(5-amidino-3-indolyl)methylene]-7-azaoxindole;
  - 69) 3-[(5-phosphono-3-indolyl)methylene]-7-azaoxindole;
  - 10 70) 3-[(5-carboxy-3-indolyl)methylene]-7-azaoxindole;
  - 71) 3-[(5-carbomethoxy-3-indolyl)methylene]-7-azaoxindole;
  - 72) 3-[(7-azaindol-3-yl)methylene]-7-azaoxindole;
  - 73) 3-[(4-hydroxy-7-azaindol-3-yl)methylene]-7-azaoxindole;
  - 74) 3-[(4-amino-7-azaindol-3-yl)methylene]-7-azaoxindole;
  - 15 75) 3-[(4-(3-piperidinopropionylamino))-7-azaindol-3-yl]  
methylene]-7-azaoxindole;
  - 76) 3-[(4-ureido-7-azaindol-3-yl)methylene]-7-azaoxindole;
  - 77) 3-[(4-sulfo-7-azaindol-3-yl)methylene]-7-azaoxindole;
  - 78) 3-[(4-sulfamoyl-7-azaindol-3-yl)methylene]-7-  
20 azaoxindole;
  - 79) 3-[(4-amidino-7-azaindol-3-yl)methylene]-7-azaoxindole;
  - 80) 3-[(4-carboxy-7-azaindol-3-yl)methylene]-7-azaoxindole;
- and the pharmaceutically acceptable salts of the above  
listed compounds.

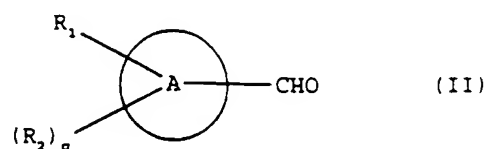
25 The compounds of the invention, and the pharmaceutically  
acceptable salts thereof, can be obtained by a process  
comprising:

- 30 a) condensation of an aldehyde of formula (II)

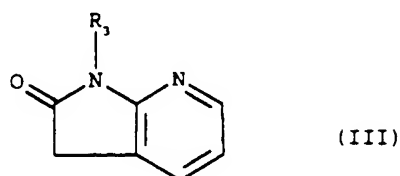
WO 96/16964

PCT/EP95/04247

-9-

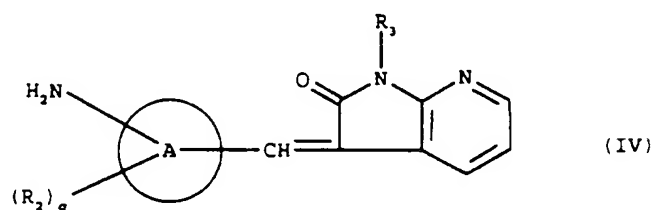


wherein A, R<sub>1</sub>, R<sub>2</sub> and q are as defined above, with a compound of formula (III)



5 wherein R<sub>3</sub> is as defined above; or

b) N-alkylation of a compound of formula (IV)



10 wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above, thus obtaining a compound of formula (I), wherein R<sub>1</sub> is -N(CH<sub>2</sub>CH<sub>2</sub>OH)<sub>2</sub> or -NHCH<sub>2</sub>(CHOH)<sub>n</sub>CH<sub>2</sub>OH and A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above; or

15 c) N-acetylation of a compound of formula (IV), wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above, thus obtaining a compound of formula (I) wherein R<sub>1</sub> is -NHCO(CHOH)<sub>n</sub>CH<sub>2</sub>OH

or  $\text{-NHCO(CH}_2\text{)}_p\text{-N}$  and A, R<sub>2</sub>, R<sub>3</sub>, n, p, q and Z are as defined above; or

WO 96/16964

PCT/EP95/04247

-10-

d) N-sulfonylation of a compound of formula (IV) wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above, thus obtaining a compound of formula (I) wherein R<sub>1</sub> is -NHSO<sub>2</sub>R<sub>9</sub> and A, R<sub>2</sub>, R<sub>3</sub>, R<sub>9</sub> and q are as defined above; or

5

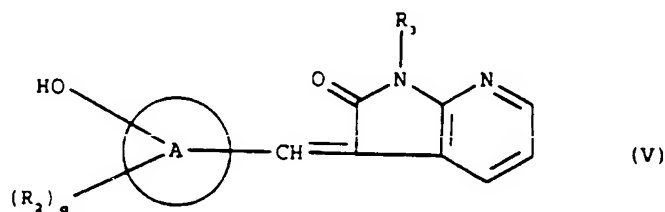
e) N-amidination of a compound of formula (IV) wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above, thus obtaining a compound of formula (I) wherein R<sub>1</sub> is -NHC(NH<sub>2</sub>)=NH and A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above; or

10

f) N-carbamoylation of a compound of formula (IV) wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above, thus obtaining a compound of formula (I) wherein R<sub>1</sub> is -NHCONH<sub>2</sub> and A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above; or

15

g) O-alkylation of a compound of formula (V)



wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above, thus obtaining a compound of formula (I) wherein R<sub>1</sub> is

20 -OCH<sub>2</sub>(CHOH)<sub>n</sub>CH<sub>2</sub>OH or -OR<sub>10</sub> in which R<sub>10</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl and A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above; or

h) O-acylation of a compound of formula (V) wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above, thus obtaining a compound of formula (I) wherein R<sub>1</sub> is -OOC(CHOH)<sub>n</sub>CH<sub>2</sub>OH or -OR<sub>10</sub> in which R<sub>10</sub> is C<sub>2</sub>-C<sub>6</sub> alkanoyl and A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above; or

25

WO 96/16964

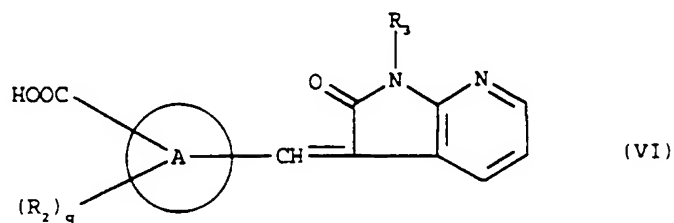
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-11-

- i) O-phosphorylation of a compound of formula (V) wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above, thus obtaining a compound of formula (I) wherein R<sub>1</sub> is -OPO(OH)<sub>2</sub> and A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above; or

5

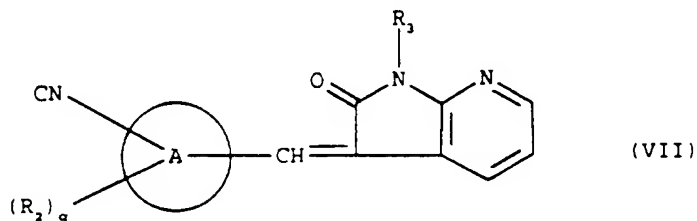
- k) esterification of a compound of formula (VI)



wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above, thus obtaining a compound of formula (I) wherein R<sub>1</sub> is -COOR<sub>6</sub> and A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above; or

10

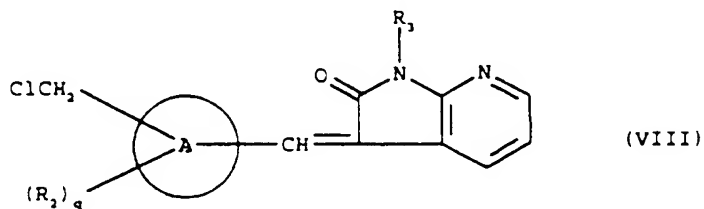
- l) ammonia addition of a compound of formula (VII)



wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above, thus obtaining a compound of formula (I) wherein R<sub>1</sub> is -C(NH<sub>2</sub>)=NH and A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above; or

15

- m) amination of a compound of formula (VIII)

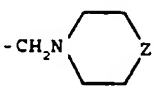


WO 96/16964

PCT/EP95/04247

-12-

wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above, thus obtaining a compound of formula (I) wherein R<sub>1</sub> is -CH<sub>2</sub>NH<sub>2</sub>

or  and A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above;

- 5 and/or conversion of a compound of formula (I) into another compound of formula (I) and/or optional salification of a compound of formula (I) or conversion of a salt into the corresponding free compound of formula (I) and/or, if desired, separation of a mixture  
10 of isomers into the single isomers.

The condensation of a compound of formula (II) with a compound of formula (III) according to process step a) may be carried out using known methods, e.g. under the  
15 condition of the Knoevenagel reaction as described e.g. by G. Jones in Organic Reactions 15, 204 (1967). Suitable catalysts are organic bases such as pyridine, piperidine or diethylamine.

The condensation may be performed in an inert organic  
20 solvent e.g. pyridine, ethanol, methanol, benzene or dioxane at temperatures ranging from about 0°C to 100°C. Preferably the reaction is carried out in warm ethanol solution in the presence of piperidine catalyst.

- 25 The N-alkylation according to process step b) may be carried out according to known methods, e.g. as described in Houben Weyl, "Methoden der Organischen Chemie", Vol. XI/I,, page 311 (1957). Thus, in order to obtain compounds of formula (I) wherein R<sub>1</sub> is -N(CH<sub>2</sub>CH<sub>2</sub>OH)<sub>2</sub>, the aromatic

WO 96/16964

PCT/EP95/04247

-13-

amine is reacted with ethylene oxide in water, alcoholic or hydroalcoholic solution at temperatures from e.g. 0°C to 100°C. Preferably the reaction is carried out in hydroalcoholic suspension at about 70-80°C by introducing

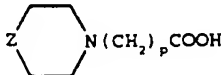
5 ethylene oxide gas. On the other hand the N-alkylation according to process step b) in order to obtain compounds of formula (I) wherein R<sub>1</sub> and/or R<sub>2</sub> is -NHCH<sub>2</sub>(CHOH)<sub>n</sub>CH<sub>2</sub>OH can be carried out by reductive amination, i.e. by condensation with an aldehyde of formula CH<sub>2</sub>OH(CHOH)<sub>n</sub>CHO in

10 the presence of a reducing agent, e.g. as described by Tietze and Eiche in "Reactions and Synthesis in the Organic Chemistry Laboratory" (1988) at page 77. Thus, to the alcoholic solution of the aromatic amine and the aldehyde is added portionwise sodium cyanoborohydride at temperature

15 ranging from 0°C to reflux temperature.

The N-acylation according to process step c) may be carried out by known methods, e.g. as described in Houben-Weyl, Vol. E5, part II, page 960 (1985). Thus, the aromatic amine

20 is reacted with the corresponding carboxylic acid of

formula CH<sub>2</sub>OH(CHOH)<sub>n</sub>COOH or , wherein Z, p and n are as defined above by using a condensing agent, such as dicyclohexylcarbodiimide (DCCD). Preferably equimolar amounts of amine, carboxylic acid and

25 dicyclohexylcarbodiimide are used in an inert solvent such as THF or benzene at temperatures from about 0°C to 50°C.

The N-sulfonylation according to process step d) may be carried out by known methods, e.g. as described in Houben-

WO 96/16964

PCT/EP95/04247

-14-

Weyl, Vol. IX, page 609 (1955). Thus, equimolar amounts of aromatic amine and sulphochloride of general formula  $R^3-SO_2-Cl$  are reacted in pyridine solution at temperatures from, e.g. 10°C to 50°C.

5

The N-amidination according to process step e) may be carried out, e.g., as described by P.D. Davis et al. in J. Med. Chem. 1992, 35, 994. Thus, the aromatic amine is treated with about 1.5 molequivalents of 3,5-dimethylpyrazole-1-carboxamidine in refluxing ethanol in the presence of about 1 molequivalents of  $NaHCO_3$ .

10

The N-carbamoylation according to process step f) may be carried out, e.g., as described in Houben-Weyl, Vol. E4, page 362 (1983). Thus the aromatic amine salt, preferably the hydrochloride salt, is reacted with an alkali metal cyanate, preferably  $NaOCN$  or  $KOCN$ , in aqueous or hydroalcoholic solution at temperature ranging, e.g., from about 50° to about 100°.

15

The O-alkylation according to process step g) may be carried out, e.g., as described in Houben-Weyl, Vol. VI/3, page 54 (1965). Thus the phenol is first transformed into an alkali metal phenolate by treatment with an alkali metal alcoholate or hydroxide or amide. Then the phenolate is reacted with a halogenide of a general formula  $XCH_2(CHOH)_nCH_2OH$  (wherein X is chlorine or bromine) in an inert solvent such as benzene or THF at temperature ranging from room to reflux temperature.

20

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WO 96/16964

PCT/EP93/04247

-15-

Preferably the reaction is carried out in benzene solution by reacting the phenol first with a stoichiometric amount of  $\text{NaNH}_2$  at room temperature and then with an excess of halogenide at reflux temperature.

5

The O-acylation according to process step h) may be carried out by known methods, e.g., as described in Houben-Weyl, Vol. VIII, page 543 (1952). Thus, the phenol is reacted with the acid halide of general formula  $\text{CH}_2\text{OH}(\text{CHOH})_n\text{COCl}$  in the presence of an organic base such as pyridine or triethylamine at temperatures ranging, e.g., from about  $0^\circ\text{C}$  to about  $50^\circ\text{C}$ . Alternatively, the phenol is reacted with the acid  $\text{CH}_2\text{OH}(\text{CHOH})_n\text{COOH}$  in the presence of a condensing agent such as dicyclohexylcarbodiimide (DCCD). Preferably 10  
15  
equimolar amounts of phenol and DCCD are used and the reaction is conducted in an inert solvent such as THF or benzene at temperatures from about  $0^\circ\text{C}$  to about  $50^\circ\text{C}$ .

The O-phosphorylation according to process step i) may be 20  
carried out by known methods, e.g., as described in Houben-Weyl, Vol. XII/2, page 143 (1962). Thus, the phenol is reacted with the phosphoric acid or a derivative thereof in water or hydroalcoholic solution at temperature ranging from room to reflux temperature. Preferably, the reaction 25  
is carried out in polyphosphoric acid (mixture of phosphoric acid and  $\text{P}_2\text{O}_5$ ) which acts as reactant and solvent at temperature ranging from about  $50^\circ\text{C}$  to about  $100^\circ\text{C}$ .

WO 96/16964

PCT/EP95/04247

-16-

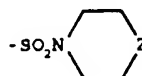
- The esterification according to process step k) may be carried out by well known methods, e.g., as described in Houben-Weyl, Vol. VIII, page 508 (1952). Thus, the mixture of acid and alcohol, dissolved in an inert solvent such as benzene or chloroform, is heated to reflux in the presence of a mineral acid such as  $H_2SO_4$ . Preferably, the water formed is removed by azeotropic distillation in a Dean-Stark condenser.
- 10 The nitril transformation according to process step l) may be carried out by known methods, e.g. as described in Houben-Weyl, Vol. 8, page 697 and 702 (1952). Thus, to the ether or chloroform solution of the nitril is added an equimolar amount of ethanol and the resulting solution is
- 15 saturated with HCl gas. The resulting iminoether hydrochloride is then transformed into amidine by reaction with ammonia in absolute ethanol at room temperature.
- The amination according to process step m) may be carried out by known methods, e.g. as described in Houben-Weyl, Vol. XI/1, page 24 (1957). Thus, a mixture of chloro-methyl compound and piperazine compound is heated to a temperature from, e.g., about 50°C to about 150°C until the reaction is complete.
- 25 The optional salification of a compound of formula (I) as well as the conversion of a salt into the corresponding free compound and the separation of a mixture of isomers into the single isomers as well as the conversion of a
- 30 compound of formula (I) into another compound of formula (I) may be carried out according to known methods.

WO 96/16964

PCT/EP95/04247

-17-

For example, the amidation of a compound of formula (I), wherein  $R_1$  is  $-\text{SO}_3\text{H}$ , so as to obtain a compound of formula



(I), wherein  $R_1$  is  $-\text{SO}_2\text{NHR}_2$ , or  
5 d).

The conversion of a compound of formula (I) in which  $R_1$  is  $-\text{SO}_3\text{H}$  into the corresponding compound of formula (I) wherein  $R_1$  is  $-\text{SO}_3\text{R}_4$  may be carried out by known  
10 esterification methods, e.g. as described above at process step k).

The conversion of a compound of formula (I) in which  $R_1$  is  $-\text{CH}_2\text{NH}_2$  into the corresponding compound of formula (I) wherein  $R_1$  is  $-\text{CH}_2\text{NH}-\text{C}(\text{NH}_2)=\text{NH}$  may be carried out by known  
15 amidination methods, e.g. as described above at process step e).

The esterification of a compound of formula (I) wherein  $R_1$  is  $-\text{CH}_2\text{OH}$  in order to obtain a compound of formula (I) wherein  $R_1$  is  $-\text{CH}_2\text{OOC}(\text{CHOH})_n\text{CH}_2\text{OH}$  may be carried out by  
20 known amidination methods, e.g. as described above at process step k).

The conversion of a compound of formula (I) in which  $R_1$  is  $-\text{CH}_2\text{OH}$  into the corresponding compound of formula (I) wherein  $R_1$  is  $-\text{CH}_2\text{OPO}(\text{OH})_2$  may be carried out by known  
25 amidination methods, e.g. as described above at process step i).

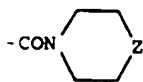
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WO 96/16964

PCT/EP95/04247

-18-

The conversion of a compound of formula (I) in which  $R_1$  is  $-\text{COOR}_6$  and wherein  $R_6$  is preferably methyl into the corresponding compound of formula (I) wherein  $R_1$  is



may be carried out by aminolysis, e.g. as described in Houben-Weyl, vol. E5, page 983 (1985). Preferably a mixture of the carbomethoxy compound and the



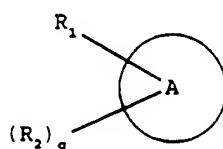
amine compound of formula is heated to reflux and the formed methanol is continuously removed by distillation.

10

The optional salification of a compound of formula (I) as well as the conversion of a salt into the free compound and the separation of a mixture of isomers into the single isomers may be carried out by conventional methods. For example, the separation of a mixture of geometric isomers, e.g. cis- and trans-isomers, may be carried out by fractional crystallization from a suitable solvent or by chromatography, either column chromatography or high pressure liquid chromatography.

20

The compounds of formula (II) may be obtained according to known methods from compounds of formula (IX)



(IX)

wherein A,  $R_1$ ,  $R_2$  and  $q$  are as defined above.

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WO 96/16964

PCT/EP95/04247

-19-

- For example the 3-formylindole derivative of formula (II) can be obtained from an indole derivative of formula (IX) wherein A is indole and  $R_1$ ,  $R_2$  and q are as defined above, by formylation with N-methylformanilide and phosphorous oxychloride according to the well known Vilsmeier-Haak method (for a review see W.G. Jackson et al. in J. Am. Chem. Soc. 1981, 103, 533). The 2-formyl-indole derivatives are obtained when the 3-position is occupied.
- 5
- 10 The 3-formyl-7-azaindole derivatives of formula (II) wherein A is 7-azaindole and  $R_1$ ,  $R_2$  and q are as defined above may be obtained by using the Vilsmeier-Haak method as described above.
- 15 Moreover, phenolic compounds of formula (II) wherein A is benzene, naphthalene or 5,6,7,8-tetrahydronaphthalene may be obtained from the corresponding phenolic compounds of formula (IX) according to the well known method of Reimer-Tiemann by reaction with chloroform and alkali hydroxides
- 20 in an aqueous or hydroalcoholic solution.
- The compounds of formula (III) are known or may be obtained by known methods from known compounds. E.g. according to Marfat and Carta (Tetrahedron Letters, 1987, 28, 4027) the
- 25 parent compound is obtained by brominating indole with pyridinium bromide perbromide to give 3,3-dibromo-7-azaindole which is then reduced to 7-azaindole with zinc in acetic acid.
- 30 A compound of formula (IV), (V), (VI), (VII) or (VIII) that is a compound of formula (I) wherein  $R_1$  is, respectively,

WO 96/16964

PCT/EP95/04247

-20-

-NH<sub>2</sub>, -OH, -COOH, -CN or -CH<sub>2</sub>Cl, may be obtained by condensation of a compound of formula (II) wherein R<sub>1</sub> is -NH<sub>2</sub>, -OH, -COOH, -CN or -CH<sub>2</sub>Cl respectively, and R<sub>2</sub> and A are as defined above, with a compound of formula (III) according to process step a).

When in the new compounds of the present invention and in the intermediate products used for their preparation groups are present which need to be protected before submitting them to the hereabove illustrated reactions, they may be protected before the reaction takes place and then deprotected at the end of the reaction, according to well known methods in organic chemistry.

The compounds of the invention possess specific tyrosine kinase inhibiting activity. It is believed that tyrosine kinase inhibitors may be of great importance in the control of uncontrolled cellular reproduction, i.e. in cellular reproduction disorders. Hence, the compounds according to the present invention can be useful in the treatment of pathological proliferation disorders in mammals, including humans. Typical examples of such disorders are tumors, including leukemia, and psoriasis. The compounds of the invention can also be useful in inhibiting the development of the atheromatous plaque and in the control of angiogenesis and as anti-metastatic agents.

Recent studies on the molecular basis of the neoplastic transformation have identified a family of genes, designed oncogenes, whose aberrant expression causes tumorigenesis. For example, the RNA tumor viruses possess such an oncogene sequence whose expression determines neoplastic conversion

WO 96/16964

PCT/EP95/04247

-21-

of infected cells. Several of their oncogene-encoded proteins, such as pp60<sup>v-src</sup>, p70<sup>gag-yes</sup>, p130<sup>gag-fps</sup> and p70<sup>gag-lgr</sup> display protein tyrosine kinase activity, that is they catalyze the transfer of the gamma-phosphate from adenosine triphosphate (ATP) to tyrosine residues in protein substrate. In normal cells, several growth factor receptors, for example the receptors for PDGF, EGF,  $\alpha$ -TGF and insulin, display tyrosine kinase activity. Binding of the growth factor (GF) activates the receptors tyrosine kinase to undergo autophosphorylation and to phosphorylate closely adjacent molecules on tyrosine. Therefore, it is thought that the phosphorylation of these tyrosine kinase receptors plays an important role in signal transduction and that the principal function of tyrosine kinase activity in normal cells is to regulate cell growth. Perturbation of this activity by oncogenic tyrosine kinases that are either overproduced and/or display altered substrate specificity may cause loss of growth control and/or neoplastic transformation. Accordingly, a specific inhibitor of tyrosine kinase can be useful in investigating the mechanism of cancerogenesis, cell proliferation and differentiations and it can be effective in the prevention and chemotherapy of cancer and in other pathological proliferative conditions, for instance as mentioned above.

The tyrosine specific protein kinase activity of the compounds of the invention is shown, e.g., by the fact that they are active in the in-vitro and in-vivo test described herebelow.

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WO 96/16964

PCT/EP95/04247

-22-

In-Vitro Assayp45 v-abl Kinase Purification

The enzyme used in our tests was the p45 v-abl tyrosine kinase which represents the catalytic domain of the Abelson tyrosine kinase (isolated from the Abelson murine leukemia virus). The p45 v-abl kinase was produced and isolated as described by Wang et al. in J. Biol. Chem. 260, 64 (1985) and by Ferguson et al. in J. Biol. Chem. 260, 3652 (1985) and in Biochem. J. 257, 321 (1989).

p45 v-abl Kinase Assay

(Val<sup>5</sup>)-Angiotensin II phosphorylation was performed by incubation with 40 ng of purified abl-kinase and ( $\gamma^{32}$ -p)-ATP, in 50  $\mu$ l of buffer containing Tris-HCl 25 mM, pH 8.0. MgCl<sub>2</sub> 10 mM and dithiothreitol 0.1 mM (kinase buffer). The reaction mixture was incubated for the indicated time at 30°C and the reaction stopped by adding 50  $\mu$ l of 5% trichloroacetic acid. After a brief incubation on ice, tubes were centrifuged. The supernatants were spotted on phosphocellulose paper squares (Whatman P-81) and washed extensively in acetic acid. The radioactivity bound to dried phosphocellulose squares was measured in a liquid scintillation counter. IC<sub>50</sub> values were calculated from triplicated determinations of each experimental point. Each inhibitor was tested at concentrations ranging from 0 to 400  $\mu$ g in the presence of fixed concentrations of peptide (2 mM) and ATP (50  $\mu$ M).

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WO 96/16964

PCT/EP95/04247

-23-

In-Vivo AssayK562 Cell Growth Inhibition Assay

K562 cells, a human myelogenous leukemia cell line, were seeded into a 24 wells tissue culture plate (Falcon 3047) (10000/well) in the presence of increasing concentrations of the compounds. After 72 h, cells were harvested and were counted using a cell counter (Coulter Counter - ZM).

The percent of inhibition was evaluated in respect to the untreated control cells.

10

The inhibitory activity data for a representative group of compounds according to the present invention, obtained both in the in-vitro p45 v-abl kinase assay and in the in vivo human chronic myeloid leukemia K562 cell growth inhibition assay described above, are set out in the following Table I.

Table I

Compound	IC <sub>50</sub> (μM)	
	v-abl	K562
3-[(7-azaindol-3-yl)methylene]-7-azaaxindole	1.04	3.89
3-[(1,4-dihydroxy-5,6,7,8-tetrahydronaphth-2-yl)methylene]-7-azaaxindole	2.14	2.36
3-[(5-methoxy-3-indolyl)methylene]-7-azaaxindole	0.03	3.21
3-[(2-methyl-3-indolyl)methylene]-7-azaaxindole	0.04	2.61

WO 96/16964

PCT/EP95/04247

-24-

In view of their high activity and low toxicity, the compounds of the invention can be used safely in medicine. For example, the approximate acute toxicity ( $LD_{50}$ ) of the compounds of the invention in the mouse, determined by  
5 single administration of increasing doses and measured on the seventh day after the treatment was found to be negligible.

The compounds of the invention can be administered in a  
10 variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar or film-coated tablets, liquid solutions or suspensions; rectally, in the form of suppositories; parenterally, e.g. intramuscularly, or by intravenous injection or infusion; or topically. The dosage  
15 depends on the age, weight, condition of the patient and administration route; for example, the dosage adopted for oral administration to adult humans may range from about 10 to about 150-200 mg per dose, from 1 to 5 times daily. Of course, these dosage regimens may be adjusted to provide  
20 the optimal therapeutic response.

The invention includes pharmaceutical compositions comprising a compound of formula (I) or pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient (which can be a  
25 carrier or diluent).

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

30 For example, the solid oral form may contain, together with the active compound, diluents, e.g., lactose, dextrose,

WO 96/16964

PCT/EP95/04247

-25-

- saccharose, cellulose, corn starch or potato starch;  
lubricant, e.g. silica, talc, stearic acid, magnesium or  
calcium stearate, and/or polyethylene glycols; binding  
agents, e.g. starches, arabic gums, gelatin,
- 5 methylcellulose, carboxymethylcellulose or polyvinyl  
pyrrolidone; disaggregating agents, e.g. a starch, alginic  
acid, alginates or sodium starch glycolate, effervescing  
mixtures; dyestuffs; sweeteners; wetting agents, such as  
lecithin, polysorbates, laurylsulphates; and, in general,
- 10 non-toxic and pharmacologically inactive substances used in  
pharmaceutical formulations. Said pharmaceutical  
preparations may be manufactured in known manner, for  
example, by means of mixing, granulating, tableting,  
sugar-coating or film-coating processes.
- 15 The liquid dispersion for oral administration may be e.g.  
syrops, emulsions and suspensions.  
The syrup may contain as carrier, for example, saccharose  
or saccharose with glycerine and/or mannitol and/or  
sorbitol.
- 20 The suspensions and the emulsions may contain as carrier,  
for example, a natural gum, agar, sodium alginate, pectin,  
methylcellulose, carboxymethylcellulose or polyvinyl  
alcohol.  
The suspensions or solutions for intramuscular injections
- 25 may contain, together with the active compound, a  
pharmaceutically acceptable carrier, e.g. sterile water,  
olive oil, ethyl oleate, glycols, e.g. propylene glycol  
and, if desired, a suitable amount of lidocaine  
hydrochloride.
- 30 The solutions for intravenous injections or infusion may  
contain as carrier, for example, sterile water or,

WO 96/16964

PCT/EP95/04247

-26-

preferable, they may be in the form of sterile aqueous, isotonic saline solutions.

The suppositories may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g.

- 5 cocoa-butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

Compositions for topical application, e.g. creams, lotions, or pastes, can be prepared by admixing the active ingredient with a conventional oleaginous or emulsifying

- 10 excipient.

A further object of the present invention is a combined method of treatment of cancer in mammals, including humans, in need of such treatment, said method comprising administering:

- 15 1) a compound of formula (I), or a pharmaceutically acceptable salt thereof, and  
2) an additional antitumor agent, in amounts and close enough together in time sufficient to produce a therapeutically useful effect.

- 20 Object of the present invention is also to provide products containing a compound of formula (I), or a pharmaceutically acceptable salt, and an additional antitumor agent as a combined preparation for simultaneous, separate or sequential use in anti-cancer therapy.

- 25 The term "antitumor agent" is meant to comprise both a single antitumor drug and "cocktails" i.e. a mixture of such drugs, according to the clinical practice.

Antitumor agents that can be formulated with a compound of the invention or alternatively, can be administered in a

- 30 combined method of treatment, can be, e.g., doxorubicin, daunomycin, epirubicin, idarubicin, etoposide,

WO 96/16964

PCT/EP95/04247

-27-

fluorouracil, melphalan, cyclophosphamide, bleomycin, vinblastine and mitomycin or a mixture of two or more thereof.

- The compounds of the invention can therefore be used in a treatment to ameliorate a cancer. They may be administered to a patient suffering from a cancer treatable with an antitumor agent, for example and anthracycline glycoside such as doxorubicin, daunomycin, epirubicin or idarubicin as mentioned above, together with the antitumor agent.
- 10 A compound of the invention and an antitumor agent such e.g. as an anthracycline glycoside can be administered to improve the condition of a patient having a leukemia such as myeloblastic leukaemia, lymphoma, sarcoma, neuroblastoma, Wilm's tumor or malignant neoplasm of the
- 15 bladder, breast, lung or thyroid.

The following examples illustrate but do not limit the invention:

20 Example 1

3-[(3,5-di-t-butyl-4-hydroxyphenyl)methylene]7-azaoindole

- A solution of 3,5-di-t-butyl-4-hydroxybenzaldehyde (2.343g, 10 mmol), 7-azaoxindole (1.341g, 10 mmol) and piperidine (0.255g, 3 mmol) in absolute ethanol (50 ml) has heated for
- 25 3 h at reflux. The reaction mixture was chilled to 5-10°C, the precipitate filtered, the residue washed with ice-cold ethanol and dried under vacuum. Almost pure title compound was so obtained in about 80% yield (0.280g).
- 30 Compound of higher purity were obtained by crystallization from ethanol.

WO 96/16964

PCT/EP95/04247

-28-

$C_{22}H_{26}N_2O_2$  calcd: C 75.40 H 7.50 N 7.99  
found: C 75.35 H 7.52 N 7.85

MS m/z 350

NMR E-isomer (DMSO)  $\delta$  1.40 (s, 3H), 6.9-7.0 (m, 1H), 7.52  
5 (s, 1H), 7.70 (s, 1H), 7.71 (bs, 1H), 7.93 (dd, J=1.7 and  
8.5 Hz, 1H), 8.07 (dd, J=1.7 and 5.1 Hz, 1H), 11.12 (s, 1H)

According to the above described procedure and starting  
from the appropriate compound of formula (II) and of  
10 formula (III), one can prepare the following compounds as  
single E- or Z-isomers, as well as their E,Z-mixtures:

3-[(1,4-dihydroxy-5,6,7,8-tetrahydronaphth-2-yl)methylene]-  
7-azaaxindole;

15  $C_{18}H_{16}N_2O_3$  calcd: C 70.12 H 5.23 N 9.08  
found: C 70.05 H 5.15 N 9.01

MS m/z 308

NMR E-isomer (DMSO)  $\delta$  1.67 (m, 4H), 6.91 (s, 1H), 6.92 (dd,  
J=5.1 and 7.6 Hz, 1H), 7.84 (s, 1H), 7.91 (dd, J=7.6 and  
20 1.5 Hz, 1H), 8.06 (dd, J=5.1 and 1.5 Hz, 1H), 8.4 (bs, 3H),  
9.01 (s, 1H), 11.10 (s, 1H)

3-[(3-hydroxy-5,6,7,8-tetrahydronaphth-2-yl)methylene]-7-  
azaaxindole;

25  $C_{18}H_{16}N_2O_2$  calcd: C 73.95 H 5.52 N 9.58  
found: C 73.66 H 5.55 N 9.45

MS m/z 292

3-[(4-quinolyl)methylene]-7-azaaxindole;

30  $C_{17}H_{11}N_3O$  calcd: C 74.71 H 4.06 N 15.38  
found: C 71.65 H 3.95 N 15.42

WO 96/16964

PCT/EP95/04247

-29-

MS m/z 273

3-[(2-methyl-3-indolyl)methylene]-7-azaaxindole;

 $C_{17}H_{13}N_3O$  calcd: C 74.17 H 4.76 N 15.26

5 found: C 74.15 H 4.66 N 15.30

MS m/z 275

NMR Z-isomer (DMSO)  $\delta$  6.79 (dd, J=7.5 and 5.0 Hz, 1H), 6.86

(dd, J=7.5 and 1.8 Hz, 1H), 6.9-7.5 (m, 4H), 7.94 (s, 1H),

7.99 (dd, J=1.8 and 5.0 Hz, 1H), 11.0 (bs, 1H), 12.0 (bs,

10 1H)

3-[(3-indolyl)methylene]-7-azaaxindole;

 $C_{16}H_{11}N_3O$  calcd: C 73.55 H 4.24 N 16.08

found: C 73.48 H 4.19 N 15.55

15 MS m/z 261

NMR Z-isomer (DMSO)  $\delta$  7.00 (dd, J=5.2 and 7.4 Hz, 1H), 7.24

(m, 2H), 7.52 (m, 1H), 8.01 (dd, J=5.2 and 1.4 Hz, 1H),

8.1-8.3 (m, 3H), 9.43 (bs, 1H), 11.1 (bs, 1H), 12.1 (bs,

1H)

20

3-[(5-methoxy-3-indolyl)methylene]-7-azaaxindole;

 $C_{17}H_{13}N_3O_2$  calcd: C 70.09 H 4.50 N 14.42

found: C 70.01 H 4.45 N 14.35

MS m/z 291

25 NMR Z-isomer (DMSO)  $\delta$  3.86 (s, 3H), 6.86 (dd, J=2.4 and 8.7

Hz, 1H), 6.99 (dd, J=5.1 and 7.6 Hz, 1H), 7.40 (d, J=8.7

Hz, 1H), 7.71 (d, J=2.4 Hz, 1H), 8.00 (dd, J=5.1 and 1.5

Hz, 1H), 8.19 (dd, J=7.6 and 1.5 Hz, 1H), 8.21 (s, 1H),

9.32 (s, 1H), 11.0 (bs, 1H), 12.0 (s, 1H).

30

3-[(7-azaindol-3-yl)methylene]-7-azaaxindole;

WO 96/16964

PCT/EP95/04247

-30-

$C_{15}H_{10}N_4O$  calcd: C 68.69 H 3.84 N 21.36  
found: C 68.65 H 3.85 N 21.25

MS m/z 262

NMR Z-isomer (DMSO)  $\delta$  7.02 (dd, J=5.3 and 7.5 Hz, 1H), 7.29  
5 (dd, J=4.5 and 7.9 Hz, 1H), 8.03 (dd, J=5.3 and 1.5 Hz, 1H), 8.16 (dd, J=7.5 and 1.5 Hz, 1H), 8.22 (s, 1H), 8.35 (dd, J=4.5 and 1.5 Hz, 1H), 8.58 (dd, J=7.9 and 1.5 Hz, 1H), 9.49 (s, 1H), 11.14 (s, 1H), 12.6 (bs, 1H).

- 10 3-[(4-hydroxyphenyl)methylene]-7-azaaxindole;  
3-[4-(2,3-dihydroxypropoxy)phenylmethylene]-7-azaaxindole;  
3-[(4-methoxyphenyl)methylene]-7-azaaxindole;  
3-[(4-aminophenyl)methylene]-7-azaaxindole;  
3-[(4-diethanolaminophenyl)methylene]-7-azaaxindole;
- 15 3-[(4-glyceroylamidophenyl)methylene]-7-azaaxindole;  
3-[4-(3-piperidinopropionylamino)phenyl)methylene]-7-azaaxindole;  
3-[(4-ureidophenyl)methylene]-7-azaaxindole;  
3-[(4-mesylaminophenyl)methylene]-7-azaaxindole;
- 20 3-[(4-guanidinophenyl)methylene]-7-azaaxindole;  
3-[(4-sulfophenyl)methylene]-7-azaaxindole;  
3-[(4-N,N-piperazinylsulfamoylphenyl)methylene]-7-azaaxindole;  
3-[(4-sulfamoylphenyl)methylene]-7-azaaxindole;
- 25 3-[(4-aminomethylphenyl)methylene]-7-azaaxindole;  
3-[(4-amidinophenyl)methylene]-7-azaaxindole;  
3-[(4-phosphonooxyphenyl)methylene]-7-azaaxindole;  
3-[(4-carboxyphenyl)methylene]-7-azaaxindole;  
3-[(4-carbomethoxyphenyl)methylene]-7-azaaxindole;
- 30 3-[(4-hydroxymethylphenyl)methylene]-7-azaaxindole;



WO 96/16964

PCT/EP95/04247

-31-

- 3-[4-(2,3-dihydroxypropylamino)phenylmethylene]-7-  
azaaxindole;  
3-[(4-glycoloyloxyphenyl)methylene]-7-azaaxindole;  
3-[(4-phosphonophenyl)methylene]-7-azaaxindole;  
5 3-[(4-hydroxyethyl-1-piperazin-1-ylmethyl)phenylmethylene]-  
7-azaaxindole;  
3-[4-(N,N-(4'-hydroxyethyl)piperazinylcarbonyl)phenyl  
methylene]-7-azaaxindole;  
3-[4-sulfophenylmethylene]-7-azaaxindole sodium salt;  
10 3-[4-aminophenylmethylene]-7-azaaxindole hydrochloride;  
3-[4-aminophenylmethylene]-7-azaaxindole trifluoroacetate;  
3-[3-(2,3-dihydroxypropoxy)-5,6,7,8-tetrahydronaphth-2-  
yl)methylene]-7-azaaxindole;  
3-[(3-methoxy-5,6,7,8-tetrahydronaphth-2-yl)methylene]-7-  
15 azaaxindole;  
3-[(4-amino-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-  
azaaxindole;  
3-[(4-diethanolamino-5,6,7,8-tetrahydronaphth-1-yl)  
methylene]-7-azaaxindole;  
20 3-[(4-glyceroylamino-5,6,7,8-tetrahydronaphth-1-yl)  
methylene]-7-azaaxindole;  
3-[4-(3-piperidinopropionylamino)-5,6,7,8-tetrahydronaphth-  
1-yl)methylene]-7-azaaxindole;  
3-[(4-ureido-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-  
25 azaaxindole;  
3-[(4-mesylamino-5,6,7,8-tetrahydronaphth-1-yl)methylene]-  
7-azaaxindole;  
3-[(4-guanidino-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-  
azaaxindole;  
30 3-[(4-sulfo-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-  
azaaxindole;

WO 96/16964

PCT/EP95/04247

-32-

- 3-[(4-N,N-piperazinylsulfamoyl-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-azaoxindole;
- 3-[(4-sulfamoyl-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-azaoxindole;
- 5 3-[(4-aminomethyl-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-azaoxindole;
- 3-[(4-amidino-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-azaoxindole;
- 3-[(4-phosphono-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-azaoxindole;
- 10 3-[(4-carboxy-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-azaoxindole;
- 3-[(4-carbomethoxy-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-azaoxindole;
- 15 3-[(8-hydroxy-5-quinolyl)methylene]-7-azaoxindole;
- 3-[(8-sulfo-5-quinolyl)methylene]-7-azaoxindole;
- 3-[(8-sulfamoyl-5-quinolyl)methylene]-7-azaoxindole;
- 3-[(8-aminomethyl-5-quinolyl)methylene]-7-azaoxindole;
- 3-[(5-hydroxy-3-indolyl)methylene]-7-azaoxindole;
- 20 3-[(5-amino-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-diethanolamino-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-glyceroylamido-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-(3-piperidinopropionylamino)-3-indolyl)methylene]-7-azaoxindole;
- 25 3-[(5-ureido-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-mesylamino-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-guanidino-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-sulfo-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-N,N-piperazinylsulfamoyl-3-indolyl)methylene]-7-azaoxindole;
- 30 3-[(5-sulfamoyl-3-indolyl)methylene]-7-azaoxindole;

WO 96/16964

PCT/EP95/04247

-33-

- 3-[(5-aminomethyl-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-amidino-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-phosphono-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-carboxy-3-indolyl)methylene]-7-azaoxindole;
- 5 3-[(5-carbomethoxy-3-indolyl)methylene]-7-azaoxindole;
- 3-[(7-azaindol-3-yl)methylene]-7-azaoxindole;
- 3-[(4-hydroxy-7-azaindol-3-yl)methylene]-7-azaoxindole;
- 3-[(4-amino-7-azaindol-3-yl)methylene]-7-azaoxindole;
- 3-[(4-(3-piperidinopropionylamino))-7-azaindol-3-yl)
- 10 methylene]-7-azaoxindole;
- 3-[(4-ureido-7-azaindol-3-yl)methylene]-7-azaoxindole;
- 3-[(4-sulfo-7-azaindol-3-yl)methylene]-7-azaoxindole;
- 3-[(4-sulfamoyl-7-azaindol-3-yl)methylene]-7-azaoxindole;
- 3-[(4-amidino-7-azaindol-3-yl)methylene]-7-azaoxindole;
- 15 3-[(4-carboxy-7-azaindol-3-yl)methylene]-7-azaoxindole.

#### Example 2

- 3-[4-(2,3-dihydroxypropylamino)phenylmethylene]-7-
- azaaxindole
- 20
- To a stirred solution of 3-(4-aminobenzylidene)-7-azaaxindole  
(2.373g, 10 mmol) in methanol (30 ml) was added anhydrous  
methylammonium chloride (0.60 g, 10 mmol). Then sodium  
cyanoborohydride (0.378 g, 6 mmol) was added in portions.
- 25 Finally, glyceraldehyde (0.901 g, 10 mmol) was added  
portionwise over 30 min and the solution stirred at room  
temperature for 50 h. Ice cold 6N HCl was added until gas  
evolution (HCN) stopped and the pH of the solution was 2.  
The methanol was evaporated in vacuo and the remaining
- 30 aqueous solution was washed with CHCl<sub>3</sub>. Solid KOH was added  
until the pH was 12. Solid NaCl was added to saturation and

WO 96/16964

PCT/EP95/04247

-34-

the solution extracted twice with  $\text{CHCl}_3$ . The  $\text{CHCl}_3$  extracts were washed with saturated  $\text{NaCl}$  solution, dried over  $\text{K}_2\text{CO}_3$  and evaporated. The residue was chromatographed on silica gel using  $\text{CHCl}_3$ -MeOH mixtures as eluant. Thus pure title compound was obtained in about 60% yield.

$\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_3$  calcd: C 65.58 H 5.51 N 13.50  
found: C 65.57 H 5.45 N 13.55

MS m/z 311

10 Example 3

3-[(4-glyceroylamidophenyl)methylene]-7-azaoxindole

To a stirred solution of 3-(4-aminobenzylidene)-7-azaoxindole (2.373 g, 10 mmol) and glyceric acid (1.061 g, 10 mmol) in benzene (200 ml) was added dicyclohexyl carbodiimide (2.063 g, 10 mmol). The resulting suspension was stirred for 1 h at 50 - 60°C and then for 3 days at room temperature. Then the N,N'-dicyclohexylurea was filtered off, the filtrate evaporated and the residue chromatographed on silica gel using  $\text{CHCl}_3$ -MeOH mixtures as eluant. Thus pure title compound was obtained in about 50% yield.

$\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_4$  calcd: C 62.76 H 4.65 N 12.92  
found: C 62.65 H 4.63 N 12.85

25 MS m/z 325

IR  $\text{cm}^{-1}$ : 3600-2500 (NH,OH), 1680 (CO), 1650 (CO), 1620 (amide)

Example 4

30 3-[(4-mesylaminophenyl)methylene]-7-azaoxindole

WO 96/16964

PCT/EP95/04247

-35-

To a stirred solution of 3-(4-aminobenzylidene)-7-azaoxindole (2.373 g, 10 mmol) in pyridine (10 ml) was added gradually mesylchloride (1.146 g, 10 mmol) at 0-5°C under cooling. The reaction mixture was stirred for about 5 h at 0-5°C and then for 15 h at room temperature.

The mixture was poured onto an ice-water mixture, the precipitate filtered off, the residue washed thoroughly with water and then chromatographed on silica gel using CHCl<sub>3</sub>-MeOH mixtures as eluant. Thus pure title compound was obtained in about 70% yield.

C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>S calcd: C 57.13 H 4.15 N 13.32 S 10.17

found: C 57.05 H 4.08 N 13.25 S 10.05

MS m/z 315

IR cm<sup>-1</sup>: 3600-3000 (NH), 1650 (CO), 1600, 1580 (C=C).

#### Example 5

3-[(4-guanidinophenyl)methylene]-7-azaoxindole

A mixture of 3-(4-aminobenzylidene)-7-azaoxyindole (2.373 g, 10 mmol) and sodium bicarbonate (0.168 g, 2 mmol) in refluxing ethanol (100 ml) was treated with 3,5-dimethylpyrazole-1-carboxamide nitrate (3.018 g, 15 mmol) for 20 h. The solvent was removed from the cooled solution, and the residue was chromatographed on silica gel with gradient elution (1 to 5% EtOH in CHCl<sub>3</sub>) to afford pure title compound in about 50% yield.

C<sub>17</sub>H<sub>14</sub>N<sub>5</sub>O calcd: C 64.57 H 4.69 N 25.07

found: C 64.45 H 4.55 N 29.95

MS m/z 279

IR cm<sup>-1</sup>: 3600-3100 (NH), 1680 (C=NH), 1655 (CONH), 1620, 1580 (C=C).

WO 96/16964

PCT/EP95/04247

-36-

Example 6

## 3-[(4-ureidophenyl)methylene]-7-azaoxindole

5 A mixture of 3-(4-aminobenzylidene)-7-azaoxindole (2.373 g, 10 mmol) in ice water (20 ml) are added 5N HCl (2 ml, 10 mmol) under stirring. Then the mixture was heated to 70-80°C, sodium cyanate (0.715 g, 11 mmol) was added portionwise and the stirring was continued for further 4 h at this temperature.

10 After cooling the raw product was extracted with CHCl<sub>3</sub>, the organic layer washed to neutrality with saline solution, dried and evaporated in vacuo.

The residue was chromatographed on silica gel using CHCl<sub>3</sub>-MeOH mixtures as eluant to give pure title compound in  
15 about 50% yield.

C<sub>15</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub> calcd: C 64.28 H 4.32 N 19.99

found: C 64.30 H 4.25 N 19.81

MS m/z 280

IR cm<sup>-1</sup>: 3600-3000 (NH), 1660 (CO), 1645 (CO), 1610, 1590  
20 (C=C)

Example 7

## 3-[4-(2,3-dihydroxypropoxyphenyl)methylene]-7-azaoxindole

25 To a solution of 3-(4-hydroxybenzylidene)-7-azaoxindole (2.383 g, 10 mmol) in toluene (100 ml) was added portionwise under nitrogen NaH 80% (0.300 g, 10 mmol). After the salification was complete 3-chloro-1,2-propanediol (1.547 g, 14 mmol) was added and the mixture heated to  
30 reflux for 5 h.

WO 96/16964

PCT/EP95/04247

-37-

After cooling water was added, the organic phase washed and evaporated to dryness. The residue was submitted to flash chromatography using  $\text{CHCl}_3$ -MeOH mixtures as eluant to give pure title compound in about 70% yield.

5  $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4$  calcd: C 65.38 H 5.16 N 8.99  
found: C 65.25 H 5.05 N 8.85

MS m/z 312

IR  $\text{cm}^{-1}$ : 3600-2600 (NH,OH), 1660 (CO), 1610, 1580, (C=C).

10 Example 8

3-[(4-glycoloyloxyphenyl)methylene]-7-azaoxindole

To a stirred solution of 3-(4-hydroxybenzylidene)-7-azaoxindole (2,383 g, 10 mmol) in pyridine (10 ml) was  
15 added gradually glycoloyl chloride (0.945 g, 10 mmol) at 0-5°C under cooling. The reaction mixture was stirred for about 4 h at 0-5°C and then for 15 h at room temperature. The mixture was poured onto an ice-water mixture, the precipitate filtered off, the residue washed thoroughly  
20 with water and then chromatographed on silica gel using  $\text{CHCl}_3$ -MeOH mixtures as eluant. Thus pure title compound was obtained in about 60% yield.

$\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_4$  calcd: C 64.86 H 4.08 N 9.45  
found: C 64.81 H 3.98 N 9.25

25 MS m/z 296

IR  $\text{cm}^{-1}$ : 3600-2600 (NH, OH), 1740 (CO), 1660 (CO), 1620, 1580.

Example 9

30 3-[(4-phosphonoxyphenyl)methylene]-7-azaoxindole

WO 96/16964

PCT/EP95/04247

-38-

A mixture of 3-(4-hydroxybenzylidene)methylene]-7-azaoxindole (2.383 g, 10 mmol) and phosphoric acid 85 % (13 g) and phosphorus pentoxide (10 g) was heated for 2 h at 60°C. The usual work up gave the title compound in about 50 % yield.

$C_{14}H_{11}N_2O_3P$  calcd: C 52.84 H 3.48 N 8.80 P 9.73  
found: C 52.79 H 3.45 N 8.75 P 9.65

MS m/z 318

#### 10 Example 10

3-[(4-carbomethoxyphenyl)methylene]-7-azaoxindole

A solution of 3-(4-carboxybenzylidene)-7-azaoxindole (2.663 g, 10 mmol), methanol (3.2 g, 0.1 mol) and  $H_2SO_4$  95 % (1 g) in benzene (100 ml) was heated in a Soxhlet apparatus for 10 h. To dry the distillate continuously, the cap of the Soxhlet contained anhydrous  $MgSO_4$ . After cooling, water was added, the organic phase repeatedly washed with water and then evaporated under vacuum. Thus almost pure title compound was obtained in about 90% yield.

$C_{15}H_{12}N_2O_3$  calcd: C 67.16 H 4.51 N 10.44  
found: C 67.05 H 4.45 N 13.35

MS m/z 268

IR  $cm^{-1}$ : 3600-3200 (NH), 1720 (COOMe), 1660 (CO), 1620, 1600, 1580.

#### Example 11

3-[(4-amidinophenyl)methylene]-7-azaoxindole hydrochloride

To a solution of 3-(4-cyanobenzylidene)-7-azaoxindole (2.473 g, 10 mmol) in anhydrous diethylether (100 ml) a



WO 96/16964

PCT/EP95/04247

-39-

stoichiometric amount of ethanol (0.460 g, 10 mmol) was added and the solution was saturated with hydrogen chloride gas. The solution was kept overnight in the fridge in order to precipitate the iminoether hydrochloride salt.

- 5 The precipitated aminoether hydrochloride was dissolved in ethanol (50 ml) to which was added an anhydrous alcoholic ammonia solution. Thereupon the solution was kept several days at room temperature and the precipitated little amount of  $\text{NH}_4\text{Cl}$  was filtered off. The solution was evaporated in  
10 vacuum, thus obtaining almost pure title compound.

$\text{C}_{15}\text{H}_{12}\text{N}_4\text{O} \cdot \text{HCl}$  calcd: C 59.91 H 4.36 N 18.63 Cl 11.79  
found: C 59.85 H 4.25 N 18.55 Cl 11.80

MS m/z 300

15 Example 12

3-(4-hydroxyethyl-1-piperazinylmethyl)phenylmethylene]-7-azaoxindole

- A mixture of 3-(4-chloromethylbenzylidene)-7-azaoxindole  
20 (2.707 g, 10 mmol) and 4-hydroxyethylpiperazine (2.604 g, 20 mmol) in 1N NaOH (20 ml, 20 mmol) was refluxed for 48 h. The cooled reaction mixture was extracted with ether, and the ether extract was shaken with diluted hydrochloric acid. The aqueous acid layer was made alkaline with  
25 potassium carbonate and extracted with ether. Addition of hydrogen chloride to the dried ether extract precipitated a crude hydrochloride which was crystallized twice from a mixture of methanol and ether.

$\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_2\text{HCl}$  calcd: C 62.91 H 6.29 N 13.98 Cl 8.84  
30 found: C 62.85 H 6.15 N 13.85 Cl 8.75

MS m/z 400

WO 96/16964

PCT/EP95/04247

-40-

Example 13

3-[4-[N,N-(4-hydroxyethyl)piperazinylcarbamoyl]phenyl  
methylene]-7-azaoxindole

- 5 A mixture of 3-(4-carbomethoxybenzylidene)-7-azaoxindole  
(2.803 g, 10 mmol), 4-hydroxyethyl-piperazine (1.302 g, 10  
mmol) and sodium methoxide (0.540 g, 10 mmol) in benzene  
(50 ml) was heated to reflux for 10h. After cooling water  
was added cautiously, the organic phase was washed  
10 thoroughly with water and then evaporated under vacuum. The  
residue was submitted to column chromatography on silica  
gel using  $\text{CHCl}_3$ -MeOH mixtures as eluant. Thus pure title  
compound was obtained in about 60% yield.

$\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_3$  calcd: C 66.65 H 5.86 N 14.81

15 found: C 66.55 H 5.75 N 14.57

MS m/z 378

Example 14

3-[4-sulfophenylmethylene]-7-azaoxindole sodium salt

- 20 To a solution of 3-(4-sulfobenzylidene)-7-azaoxindole  
(3.206 g, 10 mmol) in 1N NaOH (10 ml, 10 mmol) was added  
isopropanol (30 ml) and the mixture was chilled under  
stirring to 0-5°C. The precipitated sodium salt was  
25 filtered, washed with ice-cooled isopropanol and dried  
under vacuum.

$\text{C}_{14}\text{H}_9\text{N}_2\text{O}_4\text{SNa}$  calcd: C 51.85 H 2.80 N 8.64 S 9.89 Na 7.09

found: C 51.75 H 2.75 N 8.60 S 9.81 Na 6.95

MS m/z 324

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WO 96/16964

PCT/EP95/04247

-41-

Example 15

3-(4-aminophenylmethylene)-7-azaoxindole hydrochloride salt

To a solution of 3-(4-aminobenzylidene)-7-azaoxindole (2.373  
5 g, 10 mmol) in ethanol (10 ml) was added 1N hydrochloridric  
acid (2 ml, 2 mmol) and the resulting mixture was  
evaporated to dryness under vacuum thus giving pure title  
compound in about 100% yield.

C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>O·HCl calcd: C 61.43 H 4.42 N 15.35 Cl 12.95  
10 found: C 61.35 H 4.39 N 15.31 Cl 12.81

MS m/z 273

Example 16

3-(4-aminophenylmethylene)-7-azaoxyindole trifluoroacetate  
15 salt

To a solution of 3-(4-aminobenzylidene)-7-azaoxindole  
(0.237 g, 1 mmol) in ethanol (10 ml) was added  
trifluoroacetic acid (0.114g, 1 mmol) and the solution was  
20 concentrated under vacuum to a small volume. Ether was  
added to precipitate the salt, the mixture was ice-cooled,  
the solid was filtered off, washed with cold ether and  
essicated under vacuum. Thus almost pure title compound was  
obtained in about 90% yield.

25 C<sub>16</sub>H<sub>12</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub> calcd: C 54.71 H 3.44 N 11.96 F 16.23  
found: C 54.65 H 3.35 N 11.85 F 16.25

MS m/z 351

Example 17

30 7-azaindol-3-carboxaledehyde

WO 96/16964

PCT/EP95/04247

-42-

A solution of 7-azaindole (23.6 g, 0.20 mol) and hexamethylenetetramine (42 g, 0.30 mol) in 33% acetic acid (84 g, 1.4 mol and 168 ml H<sub>2</sub>O) was refluxed for 6 h. The resulting clear yellow solution was diluted with water, and the product was allowed to crystallize in the refrigerator overnight. Recrystallization of the crude product from water gave almost pure title compound in 50% yield (14.9 g).

m.p. 216-218°C

10 C<sub>8</sub>H<sub>6</sub>N<sub>2</sub>O calcd: C 65.74 H 4.13 N 19.17  
found: C 65.65 H 4.05 N 19.05

MS m/z 146

Example 18

15 Tablets each weighing 0.150 g and containing 25 mg of the active substance, can be manufactured as follows:  
Composition (for 10,000 tablets):

3-[(3,5-di-t-butyl-4-hydroxyphenyl)methylen]-7-azaoxindole 250 g  
20 Lactose 800 g  
Corn starch 415 g  
Talc powder 30 g  
Magnesium stearate 5 g

25 -----

The 3-[(3,5-di-t-butyl-4-hydroxyphenyl)methylen]-7-azaoxindole, the lactose and half the corn starch are mixed; the mixture is then forced through a sieve of 0.5 mm mesh size.

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WO 96/16964

PCT/EP95/04247

-43-

Corn starch (10 g) is suspended in warm water (90 ml) and the resulting paste is used to granulate the powder. The granulate is dried, comminuted on a sieve of 1.4 mm mesh size, then the remaining quantity of starch, talc and  
5 magnesium stearate are added, carefully mixed and processed into tablets.

Example 19

Capsules, each dosed at 0.200 g and containing 20 mg of the  
10 active substance can be prepared.

Composition for 500 capsules:

	3-[(7-azaindol-3-yl)methylene]-7-azaoxindole	10 g
	Lactose	80 g
15	Corn starch	5 g
	Magnesium stearate	5 g

-----  
This formulation is encapsulated in two-piece hard gelatin capsules and dosed at 0.200 g for each capsule.

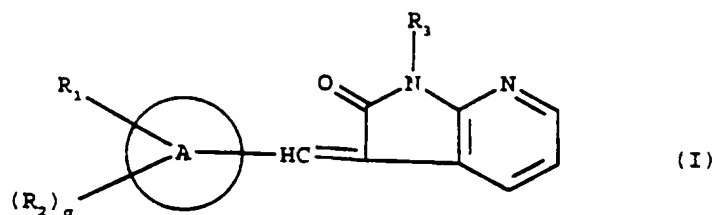
WO 96/16964

PCT/EP95/04247

-44-

# CLAIMS

1. A compound of formula (I)



5 wherein

A is benzene, naphthalene, 5,6,7,8,-tetrahydronaphthalene, quinoline, isoquinoline, indole or 7-azaindole;

$R_1$  is -H, -CN,  $-SO_3R_4$ ,  $-SO_2NHR_5$ ,  $-SO_2N$  (cyclohexyl) Z,  $-COOR_6$ ,  
 $-CON$  (cyclohexyl) Z,  
 $-CONHCH_2(CHOH)_nCH_2OH$ ,  $-NR_7R_8$ ,  $-N(CH_2CH_2OH)_2$ ,  
 $-NHCH_2(CHOH)_nCH_2OH$ ,  $-NHCONH_2$ ,  $-NH-C(NH_2)=NH$ ,  
 $-NHCO(CH_2)_p-N$  (cyclohexyl) Z,  
 $-NHCO(CHOH)_nCH_2OH$ ,  $-NHCO_2R_9$ ,  $-OR_{10}$ ,  
 $-OCH_2(CHOH)_nCH_2OH$ ,  $-OOC(CHOH)_nCH_2OH$ ,  $-OPO(OH)_2$ ,  $-CH_2NH_2$ ,  
 $-C(NH_2)=NH$ ,  $-CH_2NHC(NH_2)=NH$ ,  $-CH_2N$  (cyclohexyl) Z,  $-CH_2OH$ ,  
 $-CH_2OOC(CHOH)_nCH_2OH$ ,  $-CH_2OPO(OH)_2$  or  $-PO(OH)_2$ ;

$R_2$  is  $C_1-C_6$  alkyl, halogen, or hydroxy;

$R_3$  is -H or  $C_1-C_6$  alkyl;

$R_4$  is -H,  $C_1-C_6$  alkyl or  $-CH_2(CHOH)_nCH_2OH$ ;

$R_5$  is -H,  $C_1-C_6$  alkyl,  $-CH_2(CHOH)_nCH_2OH$  or  $-(CH_2)_mNMe_2$ ;

20  $R_6$  is -H,  $C_1-C_6$  alkyl or  $-CH_2(CHOH)_nCH_2OH$ ;

WO 96/16964

PCT/EP95/04247

-45-

each of  $R_7$  and  $R_8$  independently is  $-H$  or  $C_1-C_6$  alkyl;

$R_9$  is methyl or tolyl;

$R_{10}$  is  $-H$ ,  $C_1-C_6$  alkyl or  $C_2-C_6$  alkanoyl;

$Z$  is  $>CH_2$ ,  $>O$ ,  $>NH$  or  $>NCH_2CH_2OH$ ;

5  $n$  is zero or 1;

$m$  is 2 or 3;

$p$  is 1, 2 or 3;

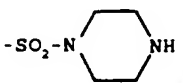
$q$  is zero, 1 or 2;

and the pharmaceutically acceptable salt thereof.

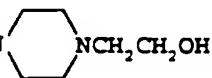
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2. A compound of formula (I) according to claim 1 wherein:

$A$  is benzene, 5,6,7,8-tetrahydronaphthalene,  
quinoline, indole or 7-azaindole;


$R_1$  is  $-H$ ,  $-NH_2$ ,  $-COOH$ ,  $-CN$ ,  $-SO_3H$ ,  $-SO_2NH_2$ , 

15

$-CON$  

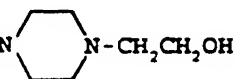
,  $-COOMe$ ,  $-N(CH_2CH_2OH)_2$ ,

$-NHCH_2CHOHCH_2OH$ ,  $-NHCONH_2$ ,  $-NHC(NH_2)=NH$ ,  $-NHCOCHOHCH_2OH$ ,

$-NHCOCH_2CH_2N$  

,  $-NHSO_2Me$ ,  $-OCH_2CHOHCH_2OH$ ,  $-OOCCH_2OH$ ,

$-OOCCHOHCH_2OH$ ,  $-OH$ ,  $-OMe$ ,  $-OPO(OH)_2$ ,  $-CH_2NH_2$ ,  $-C(NH_2)=NH$ ,

$-CH_2-N$    $-CH_2CH_2OH$

,  $-CH_2OH$ ,  $-OPO(OH)_2$ ,  $-PO(OH)_2$ ;

20

$R_2$  is  $C_1-C_6$  alkyl or hydroxy;

$R_3$  is  $-H$ ;

$q$  is zero, 1 or 2;

and the azaoxindolylidene substituent is linked to  
position 1 or 2 when  $A$  is naphthalene or 5,6,7,8-

25

tetrahydronaphthalene, to position 4 or 5 when  $A$  is

WO 96/16964

PCT/EP95/04247

-46-

quinoline, to position 3 when A is indole or 7-azaindole, whereas the R<sub>1</sub> substituent is linked to the other ring moiety when A is bicyclic, and the pharmaceutically acceptable salts thereof.

5

3. A compound which, when appropriate, may be either a Z or an E-diastereomer or a Z,E-mixture of said diastereomers, selected from a group consisting of:

10

3-[(3,5-di-tert-butyl-4-hydroxyphenyl)methylene]-7-azaoxindole;

3-[(4-hydroxyphenyl)methylene]-7-azaoxindole;

3-[4-(2,3-dihydroxypropoxy)phenylmethylene]-7-azaoxindole;

3-[(4-methoxyphenyl)methylene]-7-azaoxindole;

15

3-[(4-aminophenyl)methylene]-7-azaoxindole;

3-[(4-diethanolaminophenyl)methylene]-7-azaoxindole;

3-[(4-glyceroylamidophenyl)methylene]-7-azaoxindole;

3-[4-(3-piperidinopropionylamino)phenyl)methylene]-7-azaoxindole;

20

3-[(4-ureidophenyl)methylene]-7-azaoxindole;

3-[(4-mesylaminophenyl)methylene]-7-azaoxindole;

3-[(4-guanidinophenyl)methylene]-7-azaoxindole;

3-[(4-sulfophenyl)methylene]-7-azaoxindole;

3-[(4-N,N-piperazinylsulfamoylphenyl)methylene]-7-azaoxindole;

25

3-[(4-sulfamoylphenyl)methylene]-7-azaoxindole;

3-[(4-aminomethylphenyl)methylene]-7-azaoxindole;

3-[(4-amidinophenyl)methylene]-7-azaoxindole;

3-[(4-phosphonooxyphenyl)methylene]-7-azaoxindole;

30

3-[(4-carboxyphenyl)methylene]-7-azaoxindole;

3-[(4-carbomethoxyphenyl)methylene]-7-azaoxindole;



WO 96/16964

PCT/EP95/04247

-47-

- 3-[(4-hydroxymethylphenyl)methylene]-7-azaoxindole;  
3-[4-(2,3-dihydroxypropylamino)phenylmethylene]-7-  
azaoxindole;  
3-[(4-glycoloyloxyphenyl)methylene]-7-azaoxindole;  
5 3-[(4-phosphonophenyl)methylene]-7-azaoxindole;  
3-[(4-hydroxyethylpiperazin-1-ylmethyl)phenyl  
methylene]-7-azaoxindole;  
3-[4-(N,N-(4'-hydroxyethyl)piperazinylcarbonyl)  
phenylmethylene]-7-azaoxindole;  
10 3-[4-sulfophenylmethylene]-7-azaoxindole sodium salt;  
3-[4-aminophenylmethylene]-7-azaoxindole hydrochloride;  
3-[4-aminophenylmethylene]-7-azaoxindole trifluoro-  
acetate;  
15 3-[(3-hydroxy-5,6,7,8-tetrahydronaphth-2-yl)methylene]-  
7-azaoxindole;  
3-[(1,4-dihydroxy-5,6,7,8-tetrahydronaphth-2-yl)  
methylene]-7-azaoxindole;  
3-[3-(2,3-dihydroxypropoxy)-5,6,7,8-tetrahydronaphth-2-  
yl)methylene]-7-azaoxindole;  
20 3-[(3-methoxy-5,6,7,8-tetrahydronaphth-2-yl)methylene]-  
7-azaoxindole;  
3-[(4-amino-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-  
azaoxindole;  
3-[(4-diethanolamino-5,6,7,8-tetrahydronaphth-1-yl)  
25 methylene]-7-azaoxindole;  
3-[(4-glyceroylamino-5,6,7,8-tetrahydronaphth-1-yl)  
methylene]-7-azaoxindole;  
3-[4-(3-piperidinopropionylamino)-5,6,7,8-  
tetrahydronaphth-1-yl)methylene]-7-azaoxindole;  
30 3-[(4-ureido-5,6,7,8-tetrahydronaphth-1-yl)methylene]-  
7-azaoxindole;

WO 96/16964

PCT/EP95/04247

-48-

- 3-[(4-mesylamino-5,6,7,8-tetrahydronaphth-1-yl)  
methylene]-7-azaoxindole;
- 3-[(4-guanidino-5,6,7,8-tetrahydronaphth-1-yl)  
methylene]-7-azaoxindole;
- 5 3-[(4-sulfo-5,6,7,8-tetrahydronaphth-1-yl)methylene]-7-  
azaoxindole;
- 3-[(4-N,N-piperazinylsulfamoyl-5,6,7,8-tetrahydro  
naphth-1-yl)methylene]-7-azaoxindole;
- 10 3-[(4-sulfamoyl-5,6,7,8-tetrahydronaphth-1-yl)  
methylene]-7-azaoxindole;
- 3-[(4-aminomethyl-5,6,7,8-tetrahydronaphth-1-yl)  
methylene]-7-azaoxindole;
- 3-[(4-amidino-5,6,7,8-tetrahydronaphth-1-yl)methylene]-  
7-azaoxindole;
- 15 3-[(4-phosphono-5,6,7,8-tetrahydronaphth-1-yl)  
methylene]-7-azaoxindole;
- 3-[(4-carboxy-5,6,7,8-tetrahydronaphth-1-yl)methylene]-  
7-azaoxindole;
- 3-[(4-carbomethoxy-5,6,7,8-tetrahydronaphth-1-yl)  
20 methylene]-7-azaoxindole;
- 3-[(4-quinolyl)methylene]-7-azaoxindole;
- 3-[(8-hydroxy-5-quinolyl)methylene]-7-azaoxindole;
- 3-[(8-sulfo-5-quinolyl)methylene]-7-azaoxindole;
- 3-[(8-sulfamoyl-5-quinolyl)methylene]-7-azaoxindole;
- 25 3-[(8-aminomethyl-5-quinolyl)methylene]-7-azaoxindole;
- 3-[(2-methyl-3-indolyl)methylene]-7-azaoxindole;
- 3-[(3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-hydroxy-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-methoxy-3-indolyl)methylene]-7-azaoxindole;
- 30 3-[(5-amino-3-indolyl)methylene]-7-azaoxindole;

WO 96/16964

PCT/EP95/04247

-49-

- 3-[(5-diethanolamino-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-glyceroylamido-3-indolyl)methylene]-7-azaoxindole;
- 5 3-[(5-(3-piperidinopropionylamino)-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-ureido-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-mesylamino-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-guanidino-3-indolyl)methylene]-7-azaoxindole;
- 10 3-[(5-sulfo-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-N,N-piperazinylsulfamoyl-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-sulfamoyl-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-aminomethyl-3-indolyl)methylene]-7-azaoxindole;
- 15 3-[(5-amidino-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-phosphono-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-carboxy-3-indolyl)methylene]-7-azaoxindole;
- 3-[(5-carbomethoxy-3-indolyl)methylene]-7-azaoxindole;
- 3-[(7-azaindol-3-yl)methylene]-7-azaoxindole;
- 20 3-[(4-hydroxy-7-azaindol-3-yl)methylene]-7-azaoxindole;
- 3-[(4-amino-7-azaindol-3-yl)methylene]-7-azaoxindole;
- 3-[(4-(3-piperidinopropionylamino))-7-azaindol-3-yl)methylene]-7-azaoxindole;
- 3-[(4-ureido-7-azaindol-3-yl)methylene]-7-azaoxindole;
- 25 3-[(4-sulfo-7-azaindol-3-yl)methylene]-7-azaoxindole;
- 3-[(4-sulfamoyl-7-azaindol-3-yl)methylene]-7-azaoxindole;
- 3-[(4-amidino-7-azaindol-3-yl)methylene]-7-azaoxindole;
- 3-[(4-carboxy-7-azaindol-3-yl)methylene]-7-azaoxindole;
- 30 and the pharmaceutically acceptable salt of the above listed compounds.

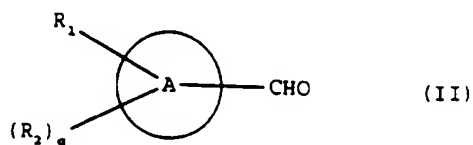
WO 96/16964

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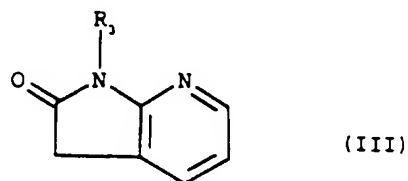
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4. A process for obtaining a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, comprising:

- 5 a) condensation of an aldehyde of formula (II)

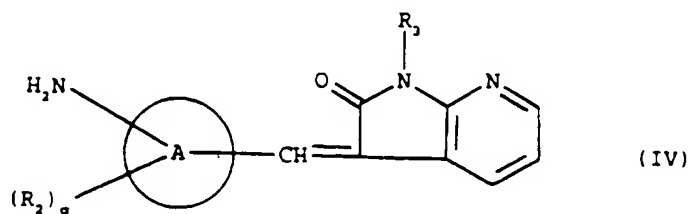


wherein A, R<sub>1</sub>, R<sub>2</sub> and q are as defined in claim 1, with a compound of formula (III)



- 10 wherein R<sub>3</sub> is as defined in claim 1; or

- b) N-alkylation of a compound of formula (IV)



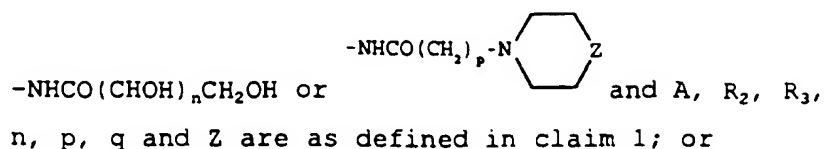
- 15 wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined in claim 1, thus obtaining a compound of formula (I), wherein R<sub>1</sub> is -N(CH<sub>2</sub>CH<sub>2</sub>OH)<sub>2</sub> or -NHCH<sub>2</sub>(CHOH)<sub>n</sub>CH<sub>2</sub>OH and A, R<sub>2</sub>, R<sub>3</sub> and q are as defined in claim 1; or

- 20 c) N-acetylation of a compound of formula (IV), wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined in claim 1, thus obtaining a compound of formula (I) wherein R<sub>1</sub> is

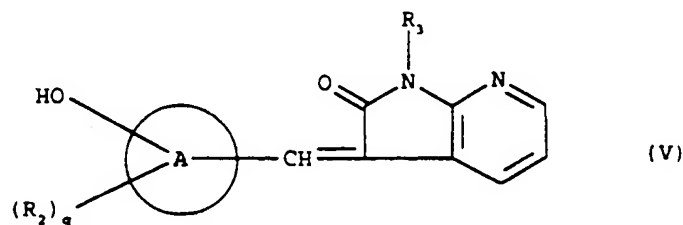
WO 96/16964

PCT/EP95/04247

-51-



- 5 d) N-sulfonylation of a compound of formula (IV) wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined in claim 1, thus obtaining a compound of formula (I) wherein R<sub>1</sub> is -NHSO<sub>2</sub>R, and A, R<sub>2</sub>, R<sub>3</sub>, R, and q are as defined above; or
- 10 e) N-amidination of a compound of formula (IV) wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined in claim 1, thus obtaining a compound of formula (I) wherein R<sub>1</sub> is -NHC(NH<sub>2</sub>)=NH and A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above; or
- 15 f) N-carbamoylation of a compound of formula (IV) wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined in claim 1, thus obtaining a compound of formula (I) wherein R<sub>1</sub> is -NHCONH<sub>2</sub> and A, R<sub>2</sub>, R<sub>3</sub> and q are as defined above; or
- 20 g) O-alkylation of a compound of formula (V)



- 25 wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined in claim 1, thus obtaining a compound of formula (I) wherein R<sub>1</sub>

WO 96/16964

PCT/EP95/04247

-52-

is  $-\text{OCH}_2(\text{CHOH})_n\text{CH}_2\text{OH}$  or  $-\text{OR}_{10}$  in which  $\text{R}_{10}$  is  $\text{C}_1\text{-C}_6$  alkyl and  $\text{A}$ ,  $\text{R}_2$ ,  $\text{R}_3$  and  $q$  are as defined above; or

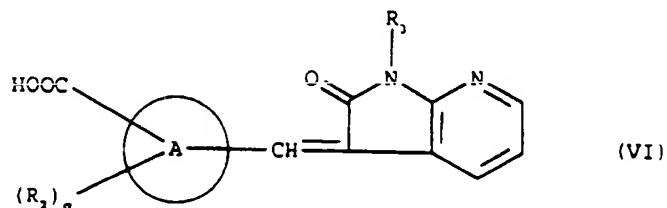
5 h) O-acylation of a compound of formula (V) wherein  $\text{A}$ ,  $\text{R}_2$ ,  $\text{R}_3$  and  $q$  are as defined in claim 1, thus obtaining a compound of formula (I) wherein  $\text{R}_1$  is  $-\text{OOC}(\text{CHOH})_n\text{CH}_2\text{OH}$  or  $-\text{OR}_{10}$  in which  $\text{R}_{10}$  is  $\text{C}_2\text{-C}_6$  alkanoyl and  $\text{A}$ ,  $\text{R}_2$ ,  $\text{R}_3$  and  $q$  are as defined above; or

10

i) O-phosphorylation of a compound of formula (V) wherein  $\text{A}$ ,  $\text{R}_2$ ,  $\text{R}_3$  and  $q$  are as defined in claim 1, thus obtaining a compound of formula (I) wherein  $\text{R}_1$  is  $-\text{OPO}(\text{OH})_2$  and  $\text{A}$ ,  $\text{R}_2$ ,  $\text{R}_3$  and  $q$  are as defined above; or

15

k) esterification of a compound of formula (VI)



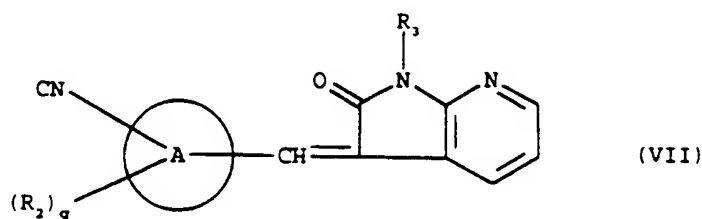
20 wherein  $\text{A}$ ,  $\text{R}_2$ ,  $\text{R}_3$  and  $q$  are as defined in claim 1, thus obtaining a compound of formula (I) wherein  $\text{R}_1$  is  $-\text{COOR}_6$  and  $\text{A}$ ,  $\text{R}_2$ ,  $\text{R}_3$  and  $q$  are as defined above; or

l) ammonia addition of a compound of formula (VII)

WO 96/16964

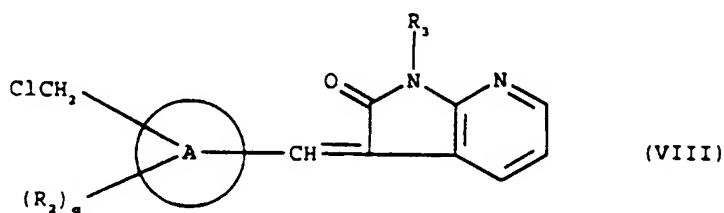
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-53-



wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined in claim 1,  
thus obtaining a compound of formula (I) wherein R<sub>1</sub>  
is -C(NH<sub>2</sub>)=NH and A, R<sub>2</sub>, R<sub>3</sub> and q are as defined  
above; or

m) amination of a compound of formula (VIII)



wherein A, R<sub>2</sub>, R<sub>3</sub> and q are as defined in claim 1,  
thus obtaining a compound of formula (I) wherein R<sub>1</sub>

is -CH<sub>2</sub>NH<sub>2</sub> or and A, R<sub>2</sub>, R<sub>3</sub> and q are as  
defined above;

and/or conversion of a compound of formula (I) into  
another compound of formula (I) and/or optional  
salification of a compound of formula (I) or  
conversion of a salt into the corresponding free  
compound of formula (I) and/or, if desired,  
separation of a mixture of isomers into the single  
isomers.

5. A pharmaceutical composition containing a suitable  
carrier and/or diluent and, as an active principle, a

WO 96/16964

PCT/EP95/04247

-54-

compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof.

- 5 6. A compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, for use as a tyrosine kinase inhibitor.
- 10 7. Use of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use as a tyrosine kinase inhibitor.
- 15 8. A compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, for use as antiproliferative agent.
- 20 9. Use of a compound of formula (I), according to claim 1, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use as antiproliferative agent.
- 25 10. A compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, for use as anti-cancer agent or in the treatment of coronary artery disease or in the control of angiogenesis.
- 30 11. Use of a compound of formula (I), according to claim 1, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use as anti-cancer agent or in the treatment of coronary artery disease or in the control of angiogenesis.



WO 96/16964

PCT/EP95/04247

-55-

12. Products containing a compound of formula (I),  
according to claim 1, or a pharmaceutically acceptable  
salt thereof, and an anti-tumor agent as a combined  
preparation for simultaneous, separate or sequential  
5 use in anti-cancer therapy.

## INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/EP 95/04247A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07D471/04 C07D519/00 A61K31/435 //(C07D471/04,221:00,  
209:00),(C07D519/00,471:00,471:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 14808 (FARMITALIA CARLO ERBA) 7 July 1994 see claims 1,6 -----	1,5,6

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \* 'A' document defining the general state of the art which is not considered to be of particular relevance
- \* 'E' earlier document but published on or after the international filing date
- \* 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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- \* 'P' document published prior to the international filing date but later than the priority date claimed

\* 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\* 'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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\* 'A' document member of the same patent family

Date of the actual completion of the international search

26 February 1996

Date of mailing of the international search report

11. 03. 96

Name and mailing address of the ISA  
European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+ 31-70) 340-3016

Authorized officer

Alfaro Faus, I

## INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No.

PCT/EP 95/04247

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA-A- 2126228	07-07-94
		CN-A- 1093707	19-10-94
		EP-A- 0626963	07-12-94
		FI-A- 943838	19-08-94
		HU-A- 67431	28-04-95
		JP-T- 7504208	11-05-95
		NZ-A- 259330	21-12-95
		PL-A- 304894	09-01-95
		US-A- 5397787	14-03-95
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